THE INCUBATION PERIOD OF BENIGN TERTIAN MALARIA

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The incubation-period of naturally-acquired benign tertian malaria is usually given as being from two to three weeks. Thus James (1920) states that the period is usually from 14 to 18 days, Stitt (1922) from 14 days, Acton cited by Castellani and Chambers (1919) 6 to 21 days, and Castellani and Chambers (1919) from 9 to 12 days. These authorities add that there are great variations in the length of the period outside the limits of the above figures. In addition, the cases of latent infection must also be remembered. In these cases several months, or even a year, may elapse since possible inoculation before the primary malarial attack develops. Often the onset is delayed until the patient undergoes some severe strain of either a mental or physical nature (James, 1920). The incubation-period of the naturally-acquired infection is thus seen to be extremely variable.

ARTIFICIALLY-INOCULATED MALARIA

(i) Mosquito-inoculations. Sir Ronald Ross (1911) gives details of cases inoculated artificially by means of infected mosquitos. The length of the incubation-period as measured by the first rise in temperature is recorded in nine instances and was found to vary from 10 to 14 to 25 days. In seven of these cases *Plasmodium vivax* was first demonstrated in from 16 to 30 days after infection.

In five general paralytics inoculated from mosquitos by Lieut.-Col. S. P. James the incubation-period varied from 11 to 16 days as regards the first definite malarial rise of temperature. In four of these cases the parasites were first found on the 17th and 18th days, three on the 17th and one on the 18th. Davidson (1925) found in a series of 23 cases that the period varied from 7 to 20 days.

In, therefore, a total of 37 cases the incubation-period, as measured by the first rise of temperature, varied from 7 to 25 days, and in 34 cases from 7 to 30 days as regards the first appearance of parasites, Davidson measuring the period by both methods.

(ii) Subcutaneous-inoculation. Most authorities give approximately corresponding lengths of time for the duration of the incubation-period when inoculation is practised subcutaneously. Thus Gerstmann (1924) states the period varies from 4 to 28 days, Scripture (1923) from 6 to 31 days, Donner (1925) from 5 to 21 days, Yorke and Macfie (1924) usually from 8 to 15 days, but with considerable variations, Worster-Drought and Beccle (1923) from 9 to 24 days and Nonne (1922) from 10 to 24 days. The table given by Pijper and Russell (1924) shows an incubation-period of from 9 to 18 days and that of McAlister (1924) from 9 to 32 days. In a series of 43 benign tertian malaria inoculations given by Grant and Silverston (1924) the first rise of temperature occurred from 1 to 18 days after inoculation, whereas parasites were first found from 6 to 22 days after. Korteweg (1924), in a series of 52 cases, found that parasites were first demonstrated in thick-films in from 5 to 21 days after inoculation.

Unfortunately, not all of the above authors state whether they define the termination of the incubation-period by the date upon which parasites were first found or by the date upon which the first increase of temperature occurred. It is, however, clear that the incubation period may be of many days' duration.

The incubation-period of a disease is that period which elapses between the admission to the body of the infecting organism and the first onset of symptoms. The latter may be subjective or objective (Gould, 1915). As the first appearance of symptoms may be objective in nature, the first day on which parasites are found in the peripheral blood-stream might be taken as the termination of the incubation-period. The disadvantage of this method, however, lies in the fact that there are so many factors to be taken into consideration when comparing the lengths of the incubation-period in different patients. At the commencement of an attack of malaria the parasites are usually comparatively few in number. In this case the day upon which the plasmodia are first found will depend upon : (*a*) whether thick or thin blood-films are used, (*b*) whether the whole or only a part of the film is examined and, if a part, which part (see below) ; and (*c*) the length of time each film is studied. In certain instances a fourth factor must be added : (*d*) the previous experience of the observer. If it were possible to

adopt general standard conditions, the method of measuring the incubation-period by the first appearance of the parasites would be of value.

With regard to the subjective symptoms it is clear that the length of the incubation-period cannot be determined by observing the occurrence of the first rigor, for many general paralytics inoculated with malaria do not shiver at all during their febrile treatment. The same applies to a subjective sensation of coldness, to sweating and to general enlargement of the spleen. The temperature, however, is raised during the initial malarial paroxysms, although, of course, parasites may be present during a relapse without fever occurring. But when the length of the incubation-period is under discussion malarial relapses do not enter into the subject. It should, however, be added that occasionally patients who have suffered from malaria previously may not develop febrile paroxysms but may show parasites for a few days. One such instance has occurred at Claybury Mental Hospital. In these cases, which are very rare, the method of recording the incubation-period by the first rise in temperature is not suitable. Now, non-inoculated general paralytics are subject, from time to time, to variations in temperature (Rudolf, 1925), and therefore an isolated elevation, or a succession of elevations, of temperature not immediately followed by typical malarial paroxysms or other definite signs of active malarial infection must not be taken as the termination of the incubation-period. As described by Korteweg (1924) and Rudolf (1924), some patients commence the attack of malaria by showing an irregularly moderately high temperature sometimes persisting for days, others by showing a series of elevations becoming progressively higher, and still others by a sudden very high elevation following a low, perhaps subnormal, temperature. Clearly, an initial rise of temperature to perhaps 100° F. in one case cannot be taken as the equivalent of a primary elevation to 105° F. in another case. To obviate this difficulty it is suggested that two rises of temperature be recorded to show the commencement of the malarial fever,—(*a*) the first elevation to 101° F. or over, and (*b*) the first to 103° F. or over. By adopting this method it is possible to tell at a glance whether a patient commenced his paroxysms suddenly or gradually. It will be observed that in this method increases of temperature under 101° F.

are not included. Now it is, of course, possible for a malarial paroxysm to show a rise of temperature of less than 101° F., but such a small rise of temperature would be extremely difficult to differentiate from an elevation accompanying the general paralysis. Rises of temperature above 101° F. are less common in untreated general paralytics.

In this connection the method adopted for recording the patient's temperature is important. From the time of inoculation the temperature should be recorded at least every four hours. Whenever it rises above normal it should be taken at least every hour, or even every ten minutes. The temperature varies so considerably within a short time that unless it is recorded very frequently the height of the fever might be missed.

The following table shows the length of the incubation-period as measured by the onset of the fever in the first 50 cases of general paralysis inoculated with *Plasmodium vivax* at Claybury Mental Hospital.

TABLE I

First rise of temp. occurring	101° F. to 102.9° F.		103° F. or over	
	No. of cases	Per cent.	No. of cases	Per cent.
Up to 10 days	23	46	19	38
From 11 to 20 days	22	44	23	46
From 21 to 30 days	5	10	8	16

The above table shows that the greater number of cases show an incubation-period of less than twenty-one days.

With regard to the first appearance of parasites, Tables IV and V show the number of days after inoculation when parasites were first found. Table IV is adapted from Korteweg (1924). This observer used the thick-film method. Table V shows the first days on which parasites were found in cases treated at Claybury Mental Hospital. Korteweg does not state that he searched the thick-films for a definite length of time and similarly the thin-films of the Claybury series were not searched during a standard time.

TABLE II. Occurrence of first rise of temperature to 101° F.

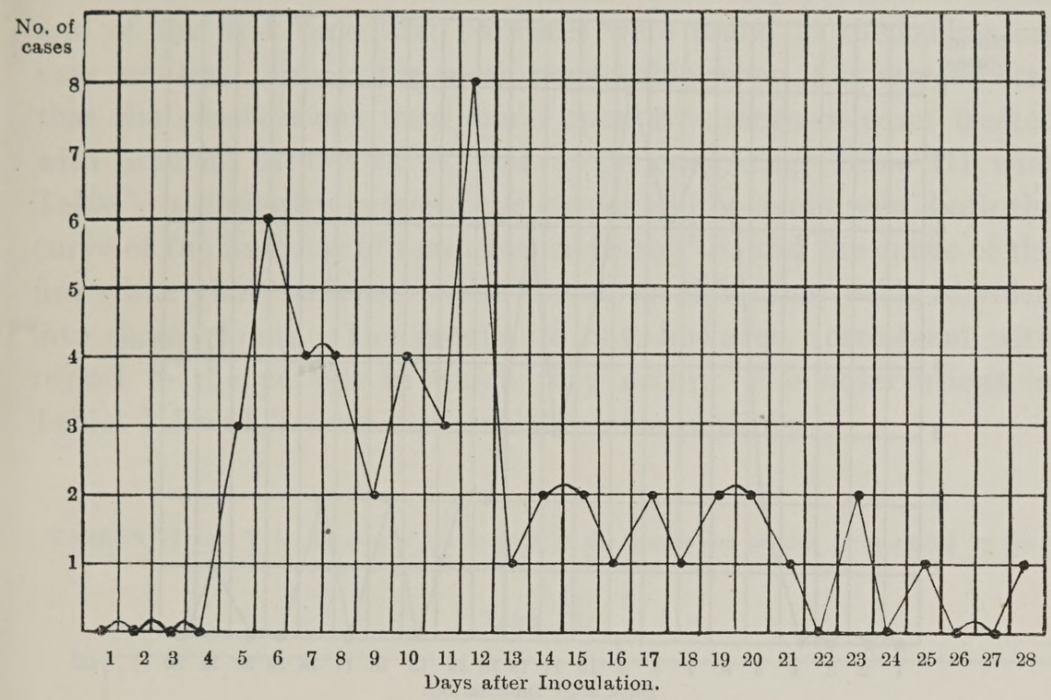


TABLE III. Occurrence of first rise of temperature to 103° F.

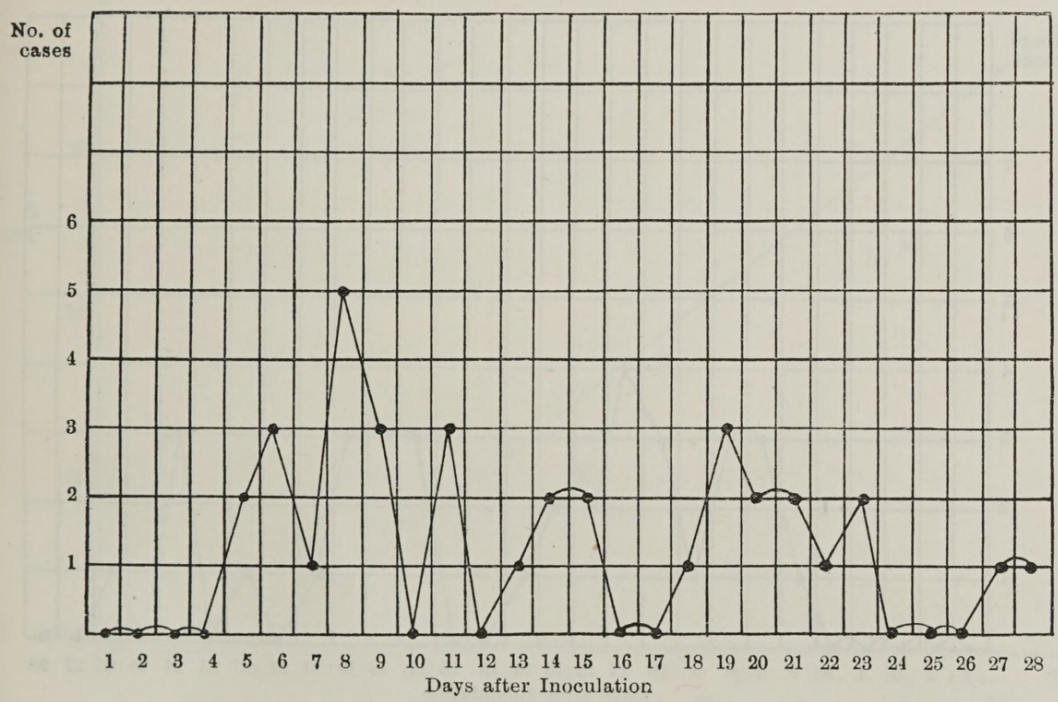


TABLE IV. First appearance of parasites in thick-films (adapted from Korteweg).

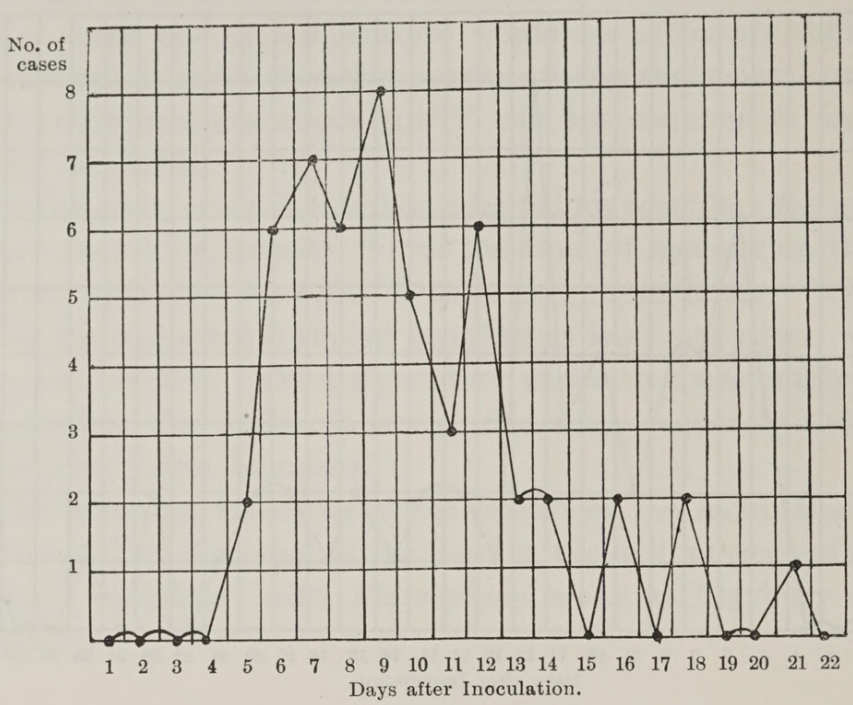
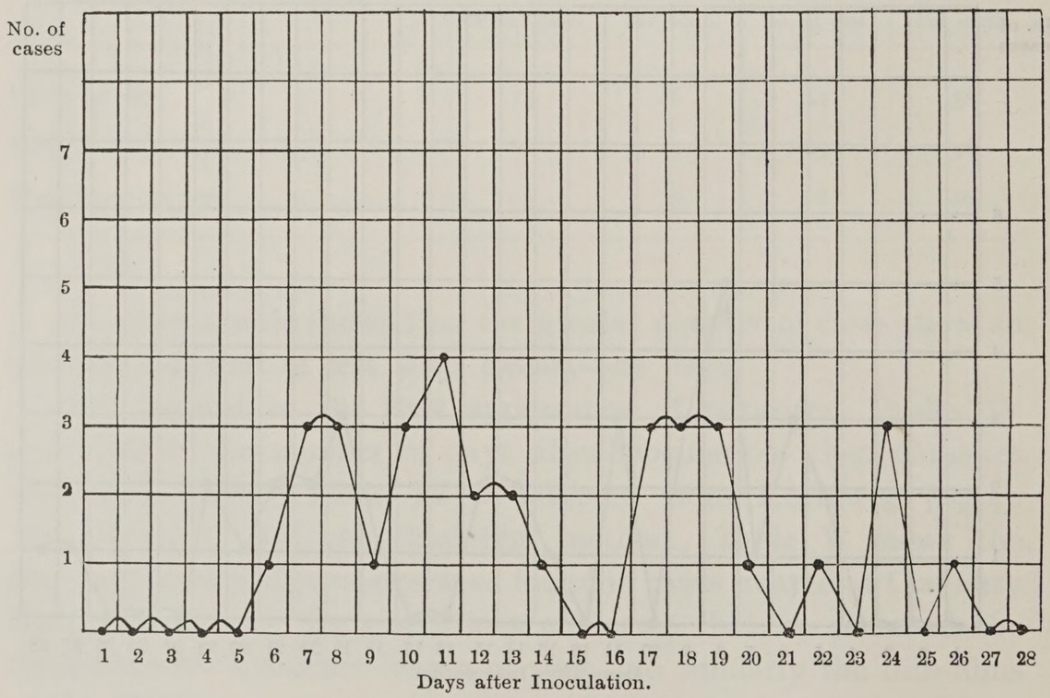


TABLE V. First appearance of parasites in thin-films.



On comparing Tables IV and V with Tables II and III it will be observed that the curves of the first rise of temperature to 101° F. and of the first time that parasites were found in thick-films are very similar. This is the more remarkable when it is remembered that the observations were made upon two series of cases treated with different strains of *P. vivax*. On comparing Table III with Table V a similarity between the curves will be again seen, both the curve of the first rise of temperature to 103° F. and the curve of the first time that parasites were found in thin-films being divided into three groups. The groups do not, however, correspond with regard to the periods in which they occur. The observations in Tables III and V were made on the same patients.

TABLES VI AND VII. Graphs of the lengths of the incubation-periods as measured by the first finding of parasites and by the first temperature-rises.

TABLE VI.

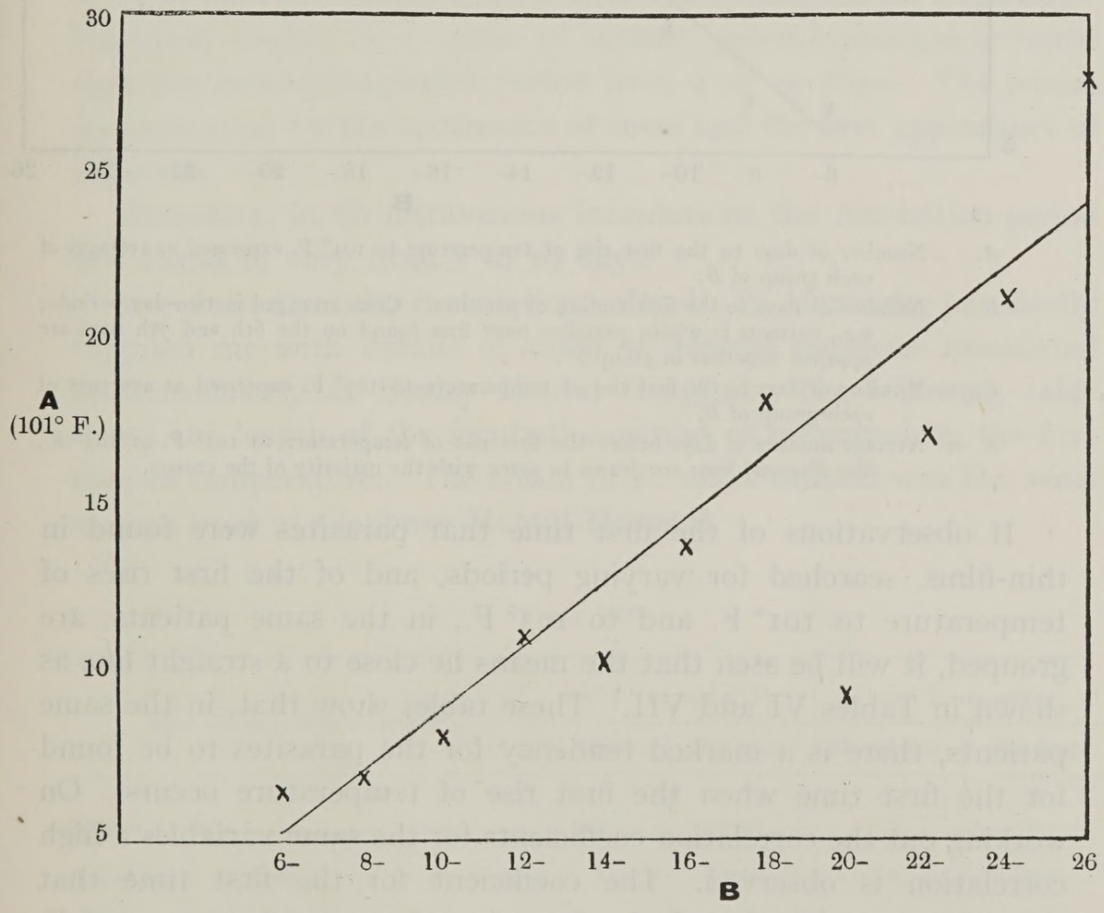
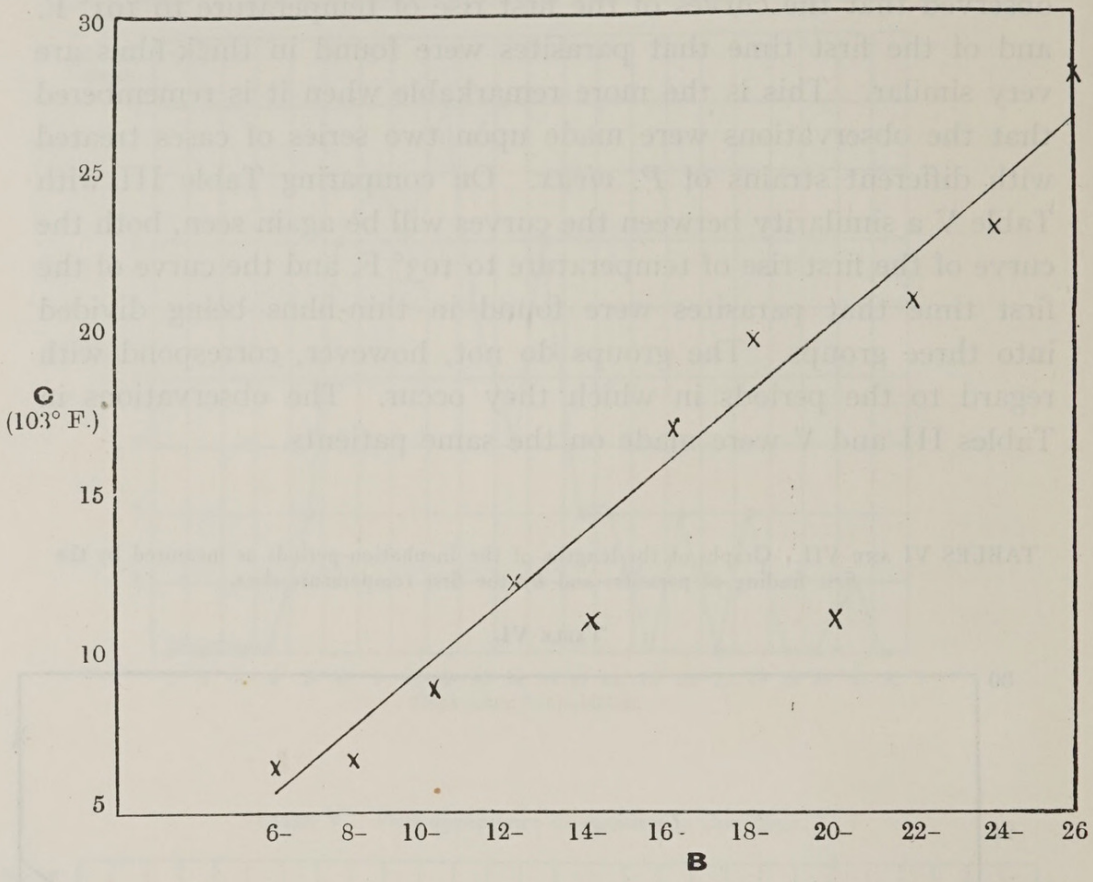


TABLE VII.



A. Number of days to the first rise of temperature to 101° F. expressed as averages of each group of *B*.

B. Number of days to the first finding of parasites. Cases arranged in two-day periods; e.g., patients in whom parasites were first found on the 6th and 7th days are grouped together in group 6–.

C. Number of days to the first rise of temperature to 103° F. expressed as averages of each group of *B*.

X = Average number of days before the first rise of temperature to 101° F. or 103° F., the diagonal lines are drawn to agree with the majority of the crosses.

If observations of the first time that parasites were found in thin-films, searched for varying periods, and of the first rises of temperature to 101° F. and to 103° F., in the same patients, are grouped, it will be seen that the means lie close to a straight line as shown in Tables VI and VII. These tables show that, in the same patients, there is a marked tendency for the parasites to be found for the first time when the first rise of temperature occurs. On working out the correlation-coefficients for the same variables a high correlation is observed. The coefficient for the first time that parasites were found and the first rise of temperature to 101° F. is + ·9032, and that for the same first variable but the rise of

temperature to 103° F. is + ·9091. There is, therefore, little difference between the correlation-coefficients when either the first rise to 101° F. or that to 103° F. is used.

The above confirms the observation that parasites are first found when the first rise of temperature occurs.

(iii) Intravenous inoculation. The duration of the incubation-period when this method is chosen would appear to be shorter than when the injection is made subcutaneously. Sir Ronald Ross (1911) gives details of six intravenous inoculations of benign tertian malaria. In these cases fever first appeared in from 3 to 12 days and parasites were first found in from 4 to 12 days after inoculation. Templeton (1924) states that in twenty cases of dementia praecox inoculated intravenously with 2 to 3 c.c. of malarial blood the temperature usually rose the day after inoculation. Macbride and Templeton (1924) found that pyrexia usually developed on the second or third day in a series of eighteen general paralytics. In both series of cases the temperature was, as a rule, irregular for a few days. Davidson (1925), in a series of sixteen general paralytics, found that the incubation-period varied from 4 to 19 days. The period was measured by the occurrence of fever and the first appearance of parasites.

Therefore, in 60 intravenous inoculations the incubation-period was found to vary from 1 to 19 days.

(iv) Intramuscular inoculation. Dr. D. R. Alexander has kindly supplied me with details of cases of general paralysis inoculated intramuscularly at Bexley Mental Hospital. The following table shows the length of the incubation-period as measured by the first rises of temperature. The strain of *P. vivax* utilised was the same as that used at Claybury Mental Hospital.

Table VIII

First rise of temp. occurring	101° F. to 102.9° F.		103° F. or over	
	No. of cases	Per cent.	No. of cases	Per cent.
Up to 10 days	9	60.0	8	53.3
From 11 to 20 days	6	40.0	6	40.0
From 21 to 30 days	0	0.0	1	6.7

On comparing the above table with Table I it will be observed that when the same strain of parasite is used there is a tendency for the incubation-period to be slightly shorter with intramuscular inoculation than with subcutaneous. On account of the relatively small number of cases, namely fifteen, in Table VIII it is probable that the differences between the lengths of the incubation-period with the two methods of inoculation are actually smaller than appears from the tables. This is in accordance with the findings of Davidson (1925). This observer noted that in a series of 13 cases the length of the incubation-period, as measured by the first fever and the first appearance of parasites, varied from 10 to 23 days, this approximating to the incubation-period when the subcutaneous route is adopted. In the two series of a total of 28 cases the incubation-period varied from 6 to 23 days as measured by the first occurrence of fever.

DOSAGE AND INCUBATION PERIOD

The usual dose of malaria-infected blood inoculated into general paralytics is from 1 to 5 c.c., although Pijper and Russell (1924) have used 10 c.c. There can, therefore, be great variations in the quantity injected. If one patient were inoculated with 2 c.c. of blood and a second with 4 c.c. it might be expected that the incubation-period of the former patient would be twice as long as that of the latter. But as the malarial parasite is the cause of the clinical signs of malaria it is clear that the volume of blood in itself can bear no relation to the incubation-period, but that the number of parasites present in the blood is the important factor. Therefore, in order to endeavour to determine whether there is any correlation between the number of parasites injected and the length of the incubation period it is necessary to know the actual, or the comparative, number of parasites in unit volume of blood. If the comparative number is chosen then the blood for inoculation must be drawn at one time from one patient, for the numbers of parasites vary in different cases, and also in the same case at different times.

The blood should then be divided and inoculated into the patients whose incubation-periods are to be compared. The blood must be well-shaken before each inoculation or the red cells containing the parasites will sink to the bottom and the patients will not receive the correct number of red cells according to the volume of blood injected. For the same reason no more than the exact quantity of blood required for each injection must be sucked into the syringe. If more than required is in the syringe, the first patient to be inoculated may receive too few or too many erythrocytes per cubic centimetre according to whether the needle of the syringe is held pointing upwards or downwards.

The above comparative method has been used in the study of a series of cases inoculated subcutaneously with benign tertian malaria at Claybury Mental Hospital. The following method was that adopted for determining the first appearance of the parasites. Thin-films were examined daily, commencing seven days after inoculation, except in certain cases in whom the rises of temperature started before that date. After the first appearance of parasites in the films had been found in this manner, more accurate observations were made. The films taken on the day previous to the first appearance of the parasites were each examined during a standard time of thirty minutes. Particular attention was paid to the edges and to the ' tags ' of blood at the end of the film as parasites are often found in greater numbers in these situations than in the remainder of the film. Table IX shows the results obtained. The patients bracketed together were inoculated from the same patient. The total quantity of blood required was withdrawn, divided into the necessary quantities, and injected into the general paralytics to be treated. The relationship between the quantity of blood, and therefore the comparative number of parasites inoculated, and the length of the incubation-period can therefore be studied in each series of cases bracketed together. The table shows the duration of the incubation-period as measured by the date on which the first rise of temperature to 101° F. and to 103° F. occurred.

TABLE IX

Series No.	Patients No.	Sex	Dose in c.cs.	In Days		
				Parasites first found	1st Temp. to 101° F.	1st Temp. to 103° F.
1	1	M	2	17	17	17
	1A	M	2	13	9	9
2	2	M	2	14	11	13
	2A	M	2	16	19	19
3	3	M	1.5	7	7	10
	3A	F	1.5	5	7	8
4	4	M	3	19	21	22
	4A	F	3	19	18	18
5	5	M	5	12	8	9
	5A	F	5	26	26	29
6	6	M	5	6	5	6
	6A	F	4.5	8	6	6
7	7	M	3	18	20	20
	7A	F	5	11	6	8
8	8	M	2.1	9	8	9
	8A	M	4	6	7	8
9	9	M	2	11	6	8
	9A	M	3	11	6	6
	9B	M	4	7	6	11
	9C	M	5	7	8	10
10	10	M	2	21	17	19
	10A	F	4	16	15	15
	10B	M	8	13	12	14

The above table may be divided into two groups: the first consists of the series Nos. 1 to 5, the patients in each series being given the same number of parasites; the second consists of the series Nos. 6 to 10, the patients in each series being given different

numbers of parasites. Series Nos. 1 to 4 show that when there is the same dosage of parasites the length of the incubation-period is somewhat similar in each series. In series Nos. 1, 2, and 4, it is more nearly similar when it is measured by the time that parasites were first found than by the first rises of temperature. In series No. 5 there is a marked difference between the length of the period in the two patients. Patient 5A had been inoculated previously with malaria but had not 'taken.' The resistance of this patient was presumably high. After the second inoculation, however, all the parasites could not have been destroyed but, if a large number were, the same effect would be produced as if a small number had been injected.

The later series of the table, Nos. 6 to 10, show the effect of inoculating different numbers of parasites. It will be observed that, in each series, the cases that received the smaller dose gave the longer incubation-period as measured by the first appearance of parasites. This was also found to hold when the length of the incubation-period is measured by the first rise of temperature except in one series, No. 9. In this series the patients that received the greatest number of parasites showed the longest incubation-periods as regards the first rise of temperature, but the shortest as regards the first appearance of parasites. It will also be observed that the incubation-periods measured by the first time that parasites were found agree more nearly with the dosage, in an inverse relationship, than do the same periods when measured by the first rise of temperature.

SUMMARY

(i) The incubation-period of the naturally-acquired benign tertian malaria is given by most authorities as being from 6 to 21 days with, however, wide variations.

(ii) In 34 cases (chiefly from the literature) inoculated by means of anopheline mosquitos, the incubation-period varied from 7 to 30 days as measured by the first date on which parasites were found, and, in 37 cases, from 7 to 25 days as measured by the first rise of temperature.

(iii) Subcutaneous inoculation of malarial blood gives, according to a number of writers, an incubation-period of from 1 to 32 days. A series of 50 general paralytics inoculated subcutaneously with *Plasmodium vivax* showed that 90 per cent. gave a rise of temperature of from 101° F. to 102·9° F. in less than 21 days after inoculation and 46 per cent. in less than 10 days. The first rise of temperature over 103° F. occurred within 21 days in 84 per cent. and within 10 days in 38 per cent.

(iv) Following subcutaneous inoculation there is a well-marked correlation between the first rises of temperature to 101° F. and to 103° F. and the first finding of parasites in thin-films. The frequency-curves of the first finding of parasites in thick-films and of the first rise of temperature to 101° F. are very similar, although the observations were made upon two different series of cases inoculated with two different strains of parasite. Curves of the first finding of parasites in thin-films and the first rise of temperature to 103° F., in the same series of cases, are also somewhat similar.

(v) Intravenous inoculation of malarial blood gave an incubation-period of from 1 to 19 days in a series of 60 cases collected from the literature.

(vi) In a series of 28 cases inoculated intramuscularly at Bexley and Winwick Mental Hospitals the incubation-period varied from 6 to 23 days.

(vii) In 10 series of cases injected subcutaneously with malarial blood it was found (*a*) that when similar numbers of parasites were injected the incubation-periods were of somewhat similar lengths, and (*b*) that when different numbers of parasites were injected the incubation-periods showed a marked tendency to be shortest when the dosage of parasites was the greatest. In one series of four cases this relationship did not hold as regards the first rises of temperature but only as regards the first dates on which parasites were found. In most series the length of the incubation-period as measured by the first time that parasites were found, under standard conditions, corresponded more nearly to the dosage than did the length of the period as measured by the first rises of temperature.

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